PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/47, 31/495

A1

(11) International Publication Number: **WO 96/33717**

(43) International Publication Date: 31 October 1996 (31.10.96)

(21) International Application Number: PCT/JP96/01102

(22) International Filing Date: 24 April 1996 (24.04.96)

(30) Priority Data:

7/106316	28 April 1995 (28.04.95)	JP
7/270856	19 October 1995 (19.10.95)	JP

(71) Applicant *(for all designated States except US)*: TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MAKINO, Haruhiko [JP/JP]; 17-8, Wakaba 1-chome, Inagawa-cho, Kawabe-gun, Hyogo 666-02 (JP). SOHDA, Takashi [JP/JP]; 27-20, Higashikanmaki 2-chome, Takatsuki-shi, Osaka 569 (JP).

(74) Agents: ASAHINA, Tadao et al.; Osaka Plant of Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: THERAPEUTIC COMPOSITION FOR ARTHRITIS

(57) Abstract

The present invention provides a pharmaceutical exhibiting rapidly acting and sustained anti-inflammatory analgesic action against chronic arthritis, with low prevalence of side effects. A pharmaceutical comprising a combination of a quinoline/quinazoline-series prophylactic/therapeutic agent for arthritis and rapidly acting anti-inflammatory analgesics including (1) a cyclooxygenase inhibitor, (2) a central analgesic, (3) a steroid, or (4) an anti-inflammatory enzyme agent. Exhibits excellent effect against arthritis from initial stage of administration, ensuring stable anti-inflammatory analgesic action with low prevalence of side effects even in chronic administration, provided that drug combination, administration method and dose are appropriately chosen according to symptoms.

DESCRIPTION

THERAPEUTIC COMPOSITION FOR ARTERITIS

Technical Field

The present invention relates to a pharmaceutical composition that serves well as a therapeutic agent for arthritis, especially as an anti-rheumatic agent.

Background Art

Arthritis, an inflammatory disease of the joints, occurs in various forms, such as rheumatoid arthritis and related diseases with joint inflammation.

Rheumatoid arthritis, also called chronic rheumatism, is a chronic multiple arthritis characterized by inflammatory changes in the synovial membrane of the articular capsule inner layer. Arthritic diseases such as rheumatoid arthritis are progressive, and cause joint disorders such as deformation and acampsia, often resulting in severe physical disorder due to a lack of effective treatment and subsequent deterioration.

Traditionally, these forms of arthritis have been chemotherapeutically treated with various agents, including steroids such as cortisone and other adrenocortical hormones, non-steroidal anti-inflammatory agents such as aspirin, piroxicam and indomethacin, gold agents such as aurothiomalate, antirheumatic agents such as chloroquine preparations and D-penicillamine, anti-gout agents such as colchicine, and immunosuppressors such as cyclophosphamide, azathioprine, methotrexate and levamisole. However, these drugs have drawbacks such as severe side effects hampering the drug's long-term use, a lack of anti-inflammatory effect and a failure to be effective against already-occurring arthritis.

In recent years, new prophylactic/therapeutic agents for arthritis having a quinoline/quinazoline skeleton have been increasingly appreciated for their low toxicity and

excellent prophylactic/therapeutic effect against arthritis. However, several weeks to months are required to obtain the desired effect from the use of a quinoline/quinazoline-series prophylactic/therapeutic agent for arthritis, because the radical cause of chronic arthritis is prevented and treated through improvement of immunological anomalies and action on bone and cartilage. There has therefore been a need for a solution to these problems and for the development of a therapeutic agent for arthritis showing symptomatic effect against acute inflammatory symptoms and pain.

Disclosure of Invention

The present inventors found that excellent anti-inflammatory analgesic effect against chronic arthritis can be obtained from initial treatment, and sustained safely for an extended period of time, by administering a pharmaceutical comprising a combination of a quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic agent possessing acute inflammation-suppressing and analgesic activities, providing clinical effect in 30 minutes, in 2 to 3 days or at latest within 1 week, such as ① a cyclooxygenase inhibitor, ② a central analgesic, ③ a steroid, or ④ an anti-inflammatory enzyme agent. The inventors conducted further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

(1) A pharmaceutical composition comprising a combination of a quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic agent.

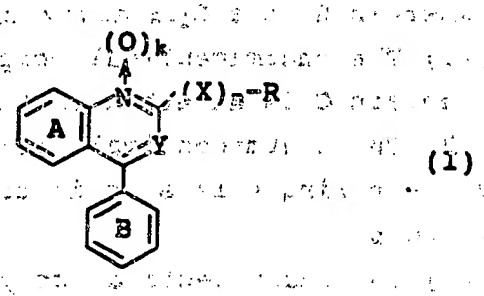
(2) The pharmaceutical composition of the above item (1), wherein said rapidly acting anti-inflammatory analgesic agent is a cyclooxygenas inhibitor.

(3) Th pharmaceutical composition of the abov item (1), wherein said rapidly acting anti-inflammatory analgesic agent is a central analgesic.

(4) The pharmaceutical composition of the above item (1), wherein said rapidly acting anti-inflammatory analgesic agent is a steroid.

(5) The pharmaceutical composition of the above item (1), wherein said rapidly acting anti-inflammatory analgesic agent is an anti-inflammatory enzyme agent.

(6) The pharmaceutical composition of the above item (1), wherein said quinoline or quinazoline compound for the prophylaxis or therapy of arthritis contains as an active ingredient a compound represented by the formula (I):



(I)

wherein Y represents a nitrogen atom or C-G (G represents a carboxyl group which may be esterified or amidated, an acyl, or a hydroxyalkyl group); R represents an optionally substituted hydrocarbon residue, or an optionally substituted heterocyclic group; X represents an oxygen atom or an optionally oxidized sulfur atom; n represents 0 or 1; k represents 0 or 1; G and R may bind together to form a ring; rings A and B may each have a substituent; or a pharmaceutically acceptable salt thereof.

(7) The pharmaceutical composition of the above item (6), wherein n represents 0 and the optionally substituted hydrocarbon residue for R is a group represented by the formula:
$-CH_2-X^1-Z^1$, wherein X^1 represents an oxygen atom, an optionally oxidized sulfur atom or $-(CH_2)_m-$ (m r presents

an integer from 0 to 5); Z^1 represents an optionally substituted hydrocarbon residue, an optionally substituted heterocyclic group or an optionally substituted amino group.

(8) The pharmaceutical composition of the above item (7), wherein X^1 is $-(CH_2)_m-$ (m is 0 or 1).

(9) The pharmaceutical composition of the above item (7), wherein the optionally substituted heterocyclic group for Z^1 is an aromatic 5-membered heterocyclic group containing 2 or 3 hetero atoms.

(10) The pharmaceutical composition of the above item (6), wherein Y is C-G.

(11) The pharmaceutical composition of the above item (10), wherein G is a C_{1-6} alkoxycarbonyl group.

(12) The pharmaceutical composition of the above item (10), wherein G is an ethoxycarbonyl group.

(13) The pharmaceutical composition of the above item (6), wherein ring A is substituted for by by at least one alkoxy group.

(14) The pharmaceutical composition of the above item (6), wherein ring A is substituted for by by two methoxy groups.

(15) The pharmaceutical composition of the above item (14), wherein ring A is substituted for by by two methoxy groups respectively at the 6- and 7-positions of the quinoline ring or quinazoline ring.

(16) The pharmaceutical composition of the above item (6), wherein ring B is substituted for by by at least one alkoxy group.

(17) The pharmaceutical composition of the above item (6), wherein ring B is substituted for by by two identical or different alkoxy groups.

(18) The pharmaceutical composition of the above item (6), wherein k is 0.

(19) The pharmaceutical composition of the above item (6), wherein the compound represented by the formula (I) is

6,7-dimethoxy-9-phenylfuro[3,4-b]quinolin-1(3H)-one;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline-3-carboxylate;

4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethylthiomethyl)-6,7-dimethoxyquinazoline;

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(4-methyl-1,2,4-triazol-3-yl)thiomethyl]quinazoline;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[2-(1-methylimidazol-2-yl)ethyl]quinoline-3-carboxylate;

methyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonylquinoline-2-acetate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-isopropoxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(4-hydroxy-3-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 7-hydroxy-6-methoxy-4-(3,4-dimethoxyphenyl)-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate 1-oxide; or

ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate.

(20) A therapeutic agent for arthritis comprising a combination of a qunoline or quinazoline compound for the prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic agent.

(21) A method of treating an arthritis and/or an inflammation in mammals which comprises administering to the mammals a therapeutically effective amount of a quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic agent.

(22) The method according to the above item (21), wherein the quinolin or quinazoline compound for the prophylaxis or therapy of arthritis and the rapidly acting

anti-inflammatory analgesic agent are administer d simultaneously.

(23) The method according to the above item (21), wherein the quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and the rapidly acting anti-inflammatory analgesic agent are administered sequentially.

(24) Use of a combination or a quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic agent to manufacture a preparation for treating an arthritis and/or an inflamation in mammals.

Best Mode for Carrying Out the Invention

Quinoline or quinazoline compound for the prophylaxis or therapy of arthritis useful for the present invention generically refer to the class of prophylactic/therapeutic agents for arthritis comprising compounds having a quinoline or quinazoline skeleton as an active ingredient. These compounds and their production methods are described in detail, for instance, in Japanese Patent Unexamined Publication (Kokai tokkyo koho) Nos. 306052/1994(EP-A-0567107), 118266/1995(EP-A-0608870), 69890/1995(EP-A-0634169), 53419/1996(EP-A-0686630) and WO95/24394. Those compounds are practically represented by the above formula (I), all possess prophylactic/therapeutic activity against arthritis and are advantageously used for the present invention.

In the above formula (I), the optionally substituted hydrocarbon residue for R is exemplified by aliphatic hydrocarbon residues, alicyclic hydrocarbon residues, alicyclic-aliphatic hydrocarbon residues, aromatic carbon ring-aliphatic hydrocarbon residues and aromatic hydrocarbon r sidues.

Such aliphatic hydrocarbon residues include saturated aliphatic hydrocarbon residues having 1 to 8 carbon atoms

(e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl, octyl); and unsaturated aliphatic hydrocarbon residues having 2 to 8 carbon atoms (e.g., vinyl (ethenyl), 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadynyl, 5-hexynyl, 1-heptynyl, 1-octynyl).

Such alicyclic hydrocarbon residues include saturated alicyclic hydrocarbon residues having 3 to 7 carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl); and unsaturated alicyclic hydrocarbon residues having 5 to 7 carbon atoms (e.g., 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2,4-cycloheptadienyl).

Such alicyclic-aliphatic hydrocarbon residues include those comprising a combination of C_{4-9} one of the above-mentioned alicyclic hydrocarbon residues and one of the above-mentioned aliphatic hydrocarbon residues (e.g., cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl, cycloheptylethyl).

Such aromatic carbon ring-aliphatic hydrocarbon residues include phenylalkyls having 7 to 9 carbon atoms (e.g., benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl); and naphthylalkyls having 11 to 13 carbon atoms (e.g., α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl).

Such aromatic hydrocarbon residues include phenyl and naphthyl (e.g., α-naphthyl, β-naphthyl).

The optionally substituted hydrocarbon residue for R is preferably a group represented by the formula:

$-CH_2-X^1-Z^1$

wherein X^1 represents an oxygen atom, an optionally oxidized sulfur atom, or $-(CH_2)_m-$ (m represents an integer from 0 to 5); Z^1 represents an optionally substituted hydrocarbon residue, an optionally substituted heterocyclic group, or an optionally substituted amino group.

The optionally oxidized sulfur atom for X^1, is exemplified by the thio group, sulfinyl group and sulfonyl group, with preference given to the thio group.

X^1 is preferably $-(CH_2)_m-$ (m represents 0, 1 or 2, preferably 0 or 1).

The optionally substituted hydrocarbon residue for Z^1 is exemplified by the same residues as those exemplifying the optionally substituted hydrocarbon residue for R mentioned above.

The heterocyclic group of the optionally substituted heterocyclic group for Z^1 is exemplified by (i) 5- to 7-membered heterocyclic groups containing 1 sulfur, nitrogen or oxygen atom; (ii) 5- or 6-membered heterocyclic groups containing 2 to 4 nitrogen atoms, and (iii) 5- or 6-membered heterocyclic groups containing 1 or 2 nitrogen atoms and 1 sulfur atom or 1 oxygen atom; these heterocyclic groups may be condensed with a 6-membered ring containing 2 or fewer nitrogen atoms, a benzene ring, or a 5-membered ring containing 1 sulfur atom.

Examples of such heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl,

1,2,4-triazol-3-yl, 1,3,4-triazol-2-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, benzpyrazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl and 1H-imidazo[4,5-b]pyrazin-2-yl.

The optionally substituted heterocyclic group for Z^1 is preferably an aromatic 5-membered heterocyclic groups containing 2 or 3 hetero atoms (e.g., oxygen atom, nitrogen atom, sulfur atom), with greater preference given to 2-imidazolyl, 1,2,4-triazol-3-yl.

In the above formula (I), the optionally substituted heterocyclic group for R is exemplified by the same groups as those exemplifying the optionally substituted heterocyclic group for Z^1 mentioned above.

In the above formula (I), the hydrocarbon residue and the heterocyclic group each represented by R or Z^1 mentioned above may have 1 to 3 substituents at any optionally substitutional positions on the ring thereof. Such substituents include aliphatic chain hydrocarbon groups, alicyclic hydrocarbon groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, halogen atoms, nitro groups, optionally substituted amino groups, optionally substituted acyl groups, optionally substituted hydroxyl groups, optionally substituted thiol groups, and optionally esterified carboxyl groups.

Aliphatic chain hydrocarbon groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include linear or branched-chain aliphatic hydrocarbon groups such as alkyl groups (preferably C_{1-10} alkyl), alkenyl groups (preferably C_{2-10} alkenyl), and alkinyl groups (preferably C_{2-10} alkinyl).

Preferable examples of the alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl,

2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl groups include vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkinyl groups include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

Alicyclic hydrocarbon groups mentioned as substituents for the hydrocarbon residue and heterocyclic group, each represented by R or Z^1, include saturated or unsaturated C_{3-8} alicyclic hydrocarbon groups such as C_{3-8} cycloalkyl groups, C_{3-8} cycloalkenyl groups and C_{4-8} cycloalkadienyl groups.

Preferable examples of the C_{3-8} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo [3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the C_{3-8} cycloalkenyl groups include those having 5 to 7 carbon atoms, such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the C_{4-8} cycloalkadienyl groups include those having 5 to 7 carbon atoms, such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Aryl groups mentioned as substituents for the hydrocarbon residue and heterocyclic group, each represent d by R or Z^1, are monocyclic or condensed polycyclic aromatic hydrocarbon groups, preferably phenyl,

naphthyl, anthryl, phenanthryl, acenaphthylenyl and oth rs, with greater preference given to phenyl, 1-naphthyl, 2-naphthyl and others.

Preferable examples of aromatic heterocyclic groups mentioned as substituents for the hydrocarbon residue and heterocyclic group, each represented by R or Z^1, include aromatic monocyclic heterocyclic groups (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl); and aromatic condensed heterocyclic groups (e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylizinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl).

Preferable examples of the non-aromatic heterocyclic groups mentioned as substituents for the hydrocarbon residue and heterocyclic group, each represented by R or Z^1, include oxylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperizinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl.

Examples of halog ns mentioned as substituents for the hydrocarbon residue and heterocyclic group, each

represented by R or Z^1, include fluorine, chlorine, bromin and iodine, with preference given to fluorine and chlorine.

Examples of the optionally substituted amino groups mentioned as substituents for the hydrocarbon residue and heterocyclic group, each represented by R or Z^1, include the amino group and substituted amino groups having 1 or 2 substituents selected from C_{1-10} alkyl groups, C_{2-10} alkenyl groups, C_{2-10} alkinyl groups, aromatic groups and so on (e.g., methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino).

Examples of the optionally substituted acyl groups mentioned as substituents for the hydrocarbon residue and heterocyclic group, each represented by R or Z^1, include formyl and groups resulting from binding of an C_{1-10} alkyl group, an C_{2-10} alkenyl group, C_{2-10} alkinyl group or an aromatic group, and a carbonyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinoyl).

Examples of the optionally substituted hydroxyl groups mentioned as substituents for the hydrocarbon residue and heterocyclic group, each represented by R or Z^1, include hydroxyl group and substituted hydroxyl groups having an appropriate substituent, particularly a substituent for use as a hydroxyl group protecting group, such as alkoxy, alkenyloxy, aralkyloxy and acyloxy, as well as aryloxy.

Said alkoxy is preferably C_{1-10} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy).

Said alk nyloxy is exemplified by C_{2-10} alkenyloxy (e.g., allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy and 2-cyclohexenylmethoxy).

Said alkinyloxy is exemplified by C_{2-10} alkinyloxy.

Said aralkyloxy is exemplified by phenyl-C_{1-4} alkyloxys (e.g., benzyloxy, phenethyloxy).

Said acyloxy is preferably an C_{2-4} alkanoyloxy (e.g., acetyloxy, propionyloxy, n-butyryloxy, isobutyryloxy).

Said aryloxy is exemplified by phenoxy and 4-chlorophenoxy.

Examples of the optionally substituted thiol groups, mentioned as substituents for the hydrocarbon residue and heterocyclic group, each represented by R or Z^1, include thiol group and substituted thiol groups having an appropriate substituent, particularly a substituent for use as a thiol group protecting group, such as alkylthio, alkenylthio, alkinylthio, aralkylthio and acylthio.

Said alkylthio is preferably C_{1-10} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio).

Said alkenylthio is preferably C_{2-10} alkenylthio.

Said alkinylthio is preferably C_{2-10} alkinylthio.

Said aralkylthio is exemplified by phenyl-C_{1-4} alkylthios (e.g., benzylthio, phenethylthio).

Said acylthio is preferably a C_{2-4} alkanoylthio (e.g., acetylthio, propionylthio, n-butyrylthio, isobutyrylthio).

Examples of the optionally esterified carboxyl groups mentioned as substituents for the hydrocarbon residue and heterocyclic group, each represented by R or Z^1, include carboxyl group, groups resulting from binding of a carboxyl group and an C_{1-6} alkyl group (e.g., methoxycarbonyl, thoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl,

tert-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl), groups resulting from binding of a carboxyl group and an C_{3-6} alkenyl group, (e.g., allyloxycarbonyl, crotyloxycarbonyl, 2-pentenyloxycarbonyl and 3-hexenyloxycarbonyl), and groups resulting from binding of a carbonyl group and an aralkyl group (e.g., benzyloxycarbonyl and phenethyloxycarbonyl).

In the above formula (I), the substituent on the hydrocarbon residue and heterocyclic group, each represented by R or Z^1, may optionally have further one or more, preferably 1 to 3, substituents at any substitutional positions. Examples of such substituents include C_{1-10} lower alkyl groups, C_{2-10} lower alkenyl groups, C_{2-10} lower alkinyl groups, C_{3-7} cycloalkyl groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, aralkyl groups (e.g., aryl-C_{1-6} alkyl), amino groups, N-mono-substituted amino groups, N,N-di-substituted amino groups, amidino groups, acyl groups, carbamoyl groups, N-mono-substituted carbamoyl groups (e.g., methylcarbamoyl, ethylcarbamoyl, phenylcarbamoyl), N,N-di-substituted carbamoyl groups (e.g., N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, piperidinocarbamoyl, morpholinocarbamoyl, etc.), sulfamoyl groups, N-mono-substituted sulfamoyl groups (e.g., methylsulfamoyl, ethylsulfamoyl, phenylsulfamoyl, p-toluenesulfamoyl), N,N-di-substituted sulfamoyl groups (e.g., N,N-dimethylsulfamoyl, N-methyl-N-phenylsulfamoyl, piperidinosulfamoyl, morpholinosulfamoyl, etc.), carboxyl groups, C_{1-10} lower alkoxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, sec-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl), hydroxyl groups, C_{1-10} lower alkoxy groups, C_{2-10} lower alkenyloxy groups, C_{3-10} cycloalkyloxy groups, lower alkylthio groups, aralkylthio groups, arylthio groups, sulfo groups, cyano groups, azide groups, halogen atoms, nitro groups and nitroso groups. These substituents are

exemplified by the same substituents as those for the hydrocarbon residu and heterocyclic group, each represented by R or Z^1.

In the above formula (I), provided that R is $-CH_2-X^1-Z^1$, the optionally substituted amino group for Z^1 is represented by $-N(R^1)(R^2)$ (R^1 and R^2, whether identical or not, represent a hydrogen atom, an optionally substituted hydrocarbon residue, or an optionally substituted heterocyclic group; or R^1 and R^2 may bind together to form a ring).

The optionally substituted hydrocarbon residue or optionally substituted heterocyclic group for R^1 or R^2 is exemplified by the same optionally substituted hydrocarbon residues or optionally substituted heterocyclic group as those mentioned to exemplify the group for R above.

The hydrocarbon residue and heterocyclic group, each represented by R^1 or R^2, may have 1 to 3 substituents at any substitutional positions on the chain or the ring thereof. Such substituents are exemplified by the same substituents as those for the hydrocarbon residue and heterocyclic group for R. These substituents on the hydrocarbon residue and heterocyclic group for R^1 or R^2 may have 1 or more, preferably 1 to 3, substituents at any substitutional positions. Examples of such substituents include C_{1-10} lower alkyl groups, C_{2-10} lower alkenyl groups, C_{2-10} lower alkinyl groups, C_{3-7} cycloalkyl groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, aralkyl groups, amino groups, N-mono-substituted amino groups, N,N-di-substituted amino groups, amidino groups, acyl groups, carbamoyl groups, N-mono-substituted carbamoyl groups, N,N-di-substituted carbamoyl groups, sulfamoyl groups, N-mono-substituted sulfamoyl groups, N,N-di-substituted sulfamoyl groups, carboxyl group, lower C_{1-10} alkoxycarbonyl groups, hydroxyl group, lower C_{1-10} alkoxy groups, low r C_{2-10} alkenyloxy groups, C_{3-8} cycloalkyloxy groups, aralkyloxy groups, aryloxy

groups, mercapto groups, lower C_{1-6} alkylthio groups, aralkylthio groups, arylthio groups, sulfo groups, cyano groups, azide groups, nitro groups, nitroso groups and halogens. These substituents are exemplified by the same substituents as those for the hydrocarbon residue and heterocyclic group, each represented by R.

R^1 and R^2 may bind together to form a ring; such $-N(R^1)(R^2)$ rings include 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrazolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 4-thiomorpholinyl, homopiperazin-1-yl, 1,2,4-triazol-1-yl, 1,3,4-triazol-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, tetrazol-1-yl, benzimidazol-1-yl, indol-1-yl and 1H-indazol-1-yl.

The optionally oxidized sulfur atom, represented by X, is exemplified by thio group, sulfinyl group and sulfonyl group, with preference given to the thio group.

In the above formula (I), rings A and B may each have a substituent. Such substituents include halogen atoms, nitro groups, optionally substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkinyl groups, optionally substituted hydroxyl groups, optionally substituted thiol groups, optionally substituted amino groups, optionally substituted acyl groups (e.g., C_{1-10} alkanoyl, C_{2-10} alkenoyl, C_{2-10} alkinoyl groups etc.), optionally esterified carboxyl groups, and optionally substituted aromatic ring groups.

Examples of the halogens mentioned as substituents for rings A and B include fluorine, chlorine, bromine and iodine, with preference given to fluorine and chlorine.

Examples of the optionally substituted C_{1-10} alkyl groups mentioned as substituents for rings A and B, may be linear C_{1-10} alkyl, branched C_{3-10} alkyl or C_{3-10} cyclic alkyl, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Examples of the optionally substituted hydroxyl groups mentioned as substituents for rings A and B, includ the hydroxyl group and substituted hydroxyl groups having an appropriate substituent, particularly a substituent for use as a hydroxyl group-protecting group, such as alkoxy, alkenyloxy, aralkyloxy and acyloxy, as well as aryloxy.

Said alkoxy is preferably a C_{1-10} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy).

Said alkenyloxy is exemplified by C_{2-10} alkenyloxys (e.g., allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy and 2-cyclohexenylmethoxy).

Said alkinyloxy is preferably a C_{2-10} alkinyloxy.

Said aralkyloxy is exemplified by phenyl-C_{1-4} alkoxy (e.g., benzyloxy, phenethyloxy).

Said acyloxy is preferably a C_{2-4} alkanoyloxy (e.g., acetyloxy, propionyloxy, n-butyryloxy, isobutyryloxy).

Said aryloxy is exemplified by phenoxy, 4-chlorophenoxy and so on.

Examples of the optionally substituted thiol groups mentioned as substituents for rings A and B, include thiol group and substituted thiol groups having an appropriate substituent, particularly a substituent for use as a thiol group-protecting group, such as alkylthio, alkenylthio, alkinylthio, aralkylthio, acylthio and arylthio.

Said alkylthio is preferably a C_{1-10} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio).

Said alkenylthio is preferably a C_{2-10} alkenylthio.

Said alkinylthio is preferably a C_{2-10} alkinylthio.

Said aralkylthio is exemplified by phenyl-C_{1-4} alkylthios (e.g., benzylthio, phenethylthio).

Said acylthio is preferably a C_{2-4} alkanoylthio (e.g., acetylthio, propionylthio, n-butyrylthio, isobutyrylthio).

Said arylthio is exemplified by phenylthio, 4-chlorophenyl, and so on.

Examples of the optionally substituted amino groups mentioned as substituents for rings A and B, include amino group and substituted amino groups having 1 or 2 substituted selected from C_{1-10} alkyl groups, C_{2-10} alkenyl groups, C_{2-10} alkinyl groups and aromatic groups and so on (e.g., methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino).

Examples of the optionally substituted acyl groups mentioned as substituents for rings A and B, include formyl and the groups resulting from binding of a C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkinyl group or aromatic group and a carbonyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinoyl).

Examples of the optionally esterified carboxyl groups mentioned as substituents for rings A and B, include carboxyl group, groups resulting from binding of a carboxyl group and a C_{1-6} alkyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl), groups resulting from binding of a carboxyl group and a C_{3-6} alkenyl group (e.g., allyloxycarbonyl, crotyloxycarbonyl, 2-pentenyloxycarbonyl and 3-hexenyloxycarbonyl), and groups resulting from

binding of a carbonyl group and an aralkyloxy group, (e.g., benzyloxycarbonyl, phenethyloxycarbonyl etc.).

Examples of the optionally substituted aromatic ring groups mentioned as substituents for rings A and B, include C_{6-14} aromatic hydrocarbon residues (e.g., phenyl, naphthyl, anthryl etc.), and heterocyclic aromatic residues (e.g., pyridyl, furyl, thienyl, imidazolyl and thiazolyl).

Such substituents for rings A and B may each be present at any substitutional position of the ring thereof; 1 to 4 identical or different substituents may be present. Provided that substituents on ring A or B are mutually adjoining, they may bind together to form a ring represented by $-(CH_2)_t-$ or $-O-(CH_2)_l-O-$ (t is an integer from 3 to 5; l is an integer from 1 to 3); such rings include 5- to 7-membered rings formed in cooperation with carbon atoms of the benzene ring.

Preferably, ring A is substituted for by at least 1 alkoxy group, preferably C_{1-3} alkoxy group, more preferably by at least 1 methoxy group. Still more preferably, ring A is substituted for by 2 identical or different alkoxy groups, preferably C_{1-3} alkoxy group, more preferably by methoxy groups. Most preferably, ring A is substituted for by 2 methoxy groups respectively at the 6- and 7-positions of the quinoline ring or quinazoline ring.

Preferably, ring B is substituted for by at least 1 alkoxy group, preferably C_{1-3} alkoxy group, more preferably at least 1 methoxy or isopropoxy group. Still more preferably, ring B is substituted for by 2 identical or different alkoxy groups, preferably C_{1-3} alkoxy group. Most preferably, ring B is substituted for by a methoxy or isopropoxy group at the 3-position and by a methoxy group at the 4-position.

In the above formula (I), provided that Y is C-G, the optionally esterified carboxyl group for G is exemplified by carboxyl group, alkoxycarbonyl groups and aralkyloxycarbonyl group.

The alkyl group in said alkoxycarbonyl groups is exemplified by C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl).

The aralkyl group in said aralkyloxycarbonyl groups is an alkyl group having an aryl group as a substituent (aryl-alkyl group). Said aryl group is exemplified by phenyl and naphthyl, each of which may have the same substituents as those for ring A above. Said alkyl group is preferably a lower C_{1-6} alkyl group. Preferable aralkyl groups include benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl)methyl and (2-naphthyl)methyl, with preference given to benzyl, phenetyl and others.

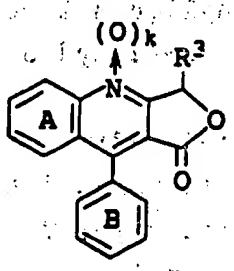
Provided that G is an amidated carboxyl group, it is represented by $-CON(R^1)(R^2)$ (R^1 and R^2 have the same definitions as those given above).

The acyl group for G in the above formula (I) is represented, for example, by the formula: $-CO-R^3$ in which R^3 is an alkyl group or an aryl group. Examples of the alkyl group for R^3 include C_{1-5} alkyl groups (e.g., methyl, ethyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, etc.). Preferred examples of the alkyl group for R^3 include methyl, butyl, isobutyl, pentyl, etc.. Examples of the aryl gorup for R^3 includes a monocyclic or condensed polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms. Preferred examples of the aryl group for R^3 include phenyl, naphthyl, anthryl, phenanthryl, etc.. In particular, phenyl, 1-naphthyl, 2-naphthyl, etc., are more preferred.

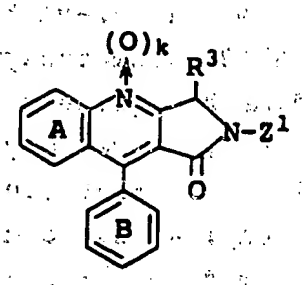
Provided that G is hydroxyalkyl, the alkyl group of the hydroxyalkyl group for G includes the above alkyl groups represented by R^1 or R^2. Preferably, the hydroxyalkyl group is represented by the formula: $-CH_2OH$ or $-CH(OH)-R^3$ in which R^3 is an defined above. R^3 in this formula is preferably methyl, ethyl, etc..

Provided that G is protected hydroxyalkyl, the protected hydroxy moiety may be the above substituted hydroxyl group as the substituent of the hydrocarbon group or heterocyclic group represented by R^1 or R^2. Preferably, the protected hydroxyalkyl group is represented by the formula: $-CH_2OCOR^4$ or $-CH(OCOR^4)-R^3$ in which R^3 is as defined above and R^4 is an alkyl group, aralkyl group or aryl group each of which may optionally be substituted. The alkyl group for R^4 includes, for example, C_{1-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.. The aralkyl group for R^4 means, for example, a C_{6-14} aryl-C_{1-4} alkyl group. Specific examples of the alkyl group in the aralkyl group include the above alkyl groups represented by R^4. specific examples of the aryl group in the aralkyl group include phenyl, naphthyl, etc. Examples of the aralkyl group include benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl)methyl, (2-naphthyl)methyl, etc.. The aryl group for R^4 includes, for example, aryl group having 6 to 14 carbon atoms such as phenyl, naphthyl, etc..

In the above formula (I), provided that Y is C-G, R and G may bind together to form a 5-membered ring. Such a structure is represented by the following formula (II) or (III).



(II)



(III)

In these formulas, R^3 repres nts a hydrogen atom, an optionally substituted hydrocarbon residue or an optionally

substituted heterocyclic group; the other symbols have the same definitions as those given above.

In the above formulas (II) and (III), the optionally substituted hydrocarbon residue and optionally substituted heterocyclic group, represented by R^3, are exemplified by the same ones mentioned to exemplify R and Z^1 above.

In the above formula (I), Y is preferably C-G, with greater preference given to a C_{1-6} alkoxycarbonyl group for G, and greatest preference given to an ethoxycarbonyl group for G.

n in the above formula (I) is preferably 0.

k in the above formula (I) is preferably 0.

Of the compounds represented by the formula (I), preference is given to those wherein Y is C-G (G is ethoxycarbonyl), R is $-CH_2-Z^1$, Z^1 is 1,2,4-triazol-1-yl, the substituents for ring A are methoxy groups each present at the 6- and 7-position of the quinoline ring, each substituent for ring B is methoxy or isopropoxy group present at the 3-position and methoxy groups present at the 4-position thereof, n is 0, and k is 0.

Preferable examples of compounds represented by the formula (I) is

6,7-dimethoxy-9-phenylfuro[3,4-b]quinoline-1(3H)-one;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline-3-carboxylate;

4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethylthiomethyl)-6,7-dimethoxyquinazoline;

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(4-methyl-1,2,4-triazol-3-yl)thiomethyl]quinazoline;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[2-(1-methylimidazol-2-yl)ethyl]quinoline-3-carboxylate;

methyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonylquinoline-2-acetate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-isopropoxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazole-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(4-hydroxy-3-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 7-hydroxy-6-methoxy-4-(3,4-dimethoxyphenyl)-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate 1-oxide; or

ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate.

The above compound (I) can be produced according to the production methods described in detail, for instance, in Japanese Patent Unexamined Publication (Kokai tokkyo koho) Nos. 306052/1994(EP-A-0567107), 118266/1995(EP-A-0608870), 69890/1995(EP-A-0634169), 53419/1996(EP-A-0686630) and WO95/24394.

The salt of compound (I) for the present invention is preferably a pharmaceutically acceptable salt, exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids.

Preferable salts with inorganic base include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt and magnesium salt; and aluminum salt and ammonium salt.

Preferable salts with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine.

Preferable salts with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid.

Preferable salts with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric

acid, oxalic acid, tartaric acid, mal ic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid.

Preferable salts with basic amino acid include salts with arginine, lysine and ornithine. Preferable salts with acidic amino acid include salts with aspartic acid and glutamic acid. Amont these salts, sodium or patassium salts are most preferable.

The compound (I) or a salt thereof of the present invention may be a hydrate.

In the present invention, the pharmaceutical agent combined with a little slowly acting quinoline or quinazoline compound for the prophylaxis or therapeuticy of arthritis is what is called a rapidly acting anti-inflammatory analgesic agent which clinically suppresses inflammation and accompanying pain in 30 minutes or in 2 to 3 days, at latest within 1 week, after administration.

As such, rapidly acting anti-inflammatory analgesics can be classified in various manners according to chemical structure, action etc., but those advantageous for use in the present invention include ① cyclooxygenase inhibitors, ② central analgesics, ③ steroids, and ④ anti-inflammatory enzyme agents.

Cyclooxygenase inhibitors are compounds that suppress cyclooxygenase 1 and/or cyclooxygenase 2; preferable examples include the following compounds and salts thereof.

Salicylic acid derivatives possessing anti-inflammatory analgesic activity, such as aspirin; pyrazolone derivatives possessing anti-inflammatory analgesic activity, such as antipyrine; phenylbutazone, oxybutazone, sulfinpyrazone, acemetacin, alclofenac, alminoprofen, anfenac, ampiroxicam, butybufen, calprofen, dichlofenac, diflunisal, droxicam, etodolac, fenbufen, fenoprofen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, indomethacin farnesil ester, ketoprofen, ketorolac, loxoprofen, mefenamic acid, meclofenamate,

meloxicam, nabumetone, naprox n, oxaprozin, pirazolac, piroxicam, pranoprofen, proglumetacin, sulindac, tenidap, tenoxicam, tiaprofenic acid, ticlopidine, tolmetin, tolfenamic acid, ximoprofen, zaltoprofen, nimesulide, fulosulide, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one, N-[2-cyclohexyloxy-4-nitrophenyl]methanesulfonamide, dihydro-4-[[3,5-bis(1,1-dimethylmethyl)-4-hydroxyphenyl]methylene]-2-methyl-2H-1,2-oxazin-3(4H)-one, 1-[4-(methylsulfonyl) phenyl]-3-tolfluoromethyl-5-(4-fluorophenyl)-1H-pyrazole, 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene, 5-bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl) phenyl]thiophene, and 5-methanesulfonamide-6-(2,4-difluorophenylthio)-1-indanone.

Also preferable are the compounds described in International Patent Publication Nos. WO95/15315, WO95/15316, WO95/15317 and WO95/15318 and salts thereof. More specifically, preferable compounds include the compounds described in claim 16 for WO95/15315 above [e.g., 1-[(4-alkylsulfonyl)phenyl]-3-substitutional-5-substitutional-1H-pyrazole derivatives], i.e.,

1-[4-(methylsulfonyl)phenyl]-5-(4-fluorophenyl)-3-trifluoromethyl-1H-pyrazole,

1-[4-(methylsulfonyl)phenyl]-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole,

1-[4-(methylsulfonyl)phenyl]-5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazole,

1-[4-(methylsulfonyl)phenyl]-5-(4-iodophenyl)-3-(trifluoromethyl)-1H-pyrazole,

1-[4-(methylsulfonyl)phenyl]-5-(phenyl)-3-(trifluoromethyl)pyrazole,

1-[4-(methylsulfonyl)phenyl]-5-(4-fluorophenyl)-3-(chlorodifluoromethyl)-1H-pyrazole,

1-[4-(methylsulfonyl)phenyl]-5-(4-chlorophenyl)-3-chlorodifluoromethyl)-1H-pyrazol ,

1-[4-(methylsulfonyl)phenyl]-5-(4-bromophenyl)-3-(chlorodifluoromethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-iodophenyl)-3-(chlorodifluoromethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(phenyl)-3-(chlorodifluoromethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-fluorophenyl)-3-(difluoromethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-bromophenyl)-3-(difluoromethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-iodophenyl)-3-(difluoromethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(phenyl)-3-(difluoromethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(fluorophenyl)-3-(pentafluoroethyl)-1H-pyrazole;
1-[4-(methylsulfonyl)phenyl]-5-(4-chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-bromophenyl)-3-(pentafluoroethyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-iodophenyl)-3-pentafluoroethyl-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(phenyl)-3-(pentafluoroethyl)pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-fluorophenyl)-3-(heptafluoropropyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-bromophenyl)-3-(heptafluoropropyl)-1H-pyrazole,
1-[4-(methylsulfonyl)phenyl]-5-(4-iodophenyl)-3-(heptafluoropropyl)-1H-pyrazole, and
1-[4-(methylsulfonyl)phenyl]-5-(phenyl)-3-(heptafluoropropyl)-1H-pyrazole;

the compounds described in claim 7 for WO95/15316 above [e.g., 4-(1H-pyrazol-1-yl)benzen sulfonamide derivatives that may be substitutional at the 3- and 5-positions], i.e.,

ethyl 1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate,

ethyl 1-[4-(aminosulfonyl)phenyl]-5-(4-methylphenyl)-1H-pyrazole-3-carboxylate,

isopropyl 1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate,

N-[4-(methylphenyl]-1-[4-(aminosulfonyl)phenyl)-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide,

N-[3-chlorophenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide,

N-[3-fluorophenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide,

N-[3-fluorophenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide,

phenylmethyl N-[[1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carbonyl]glycinate,

4-[5-(4-bromophenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide,

4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide,

4-[5-(4-chlorophenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide,

4-[3-cyano-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,

4-[3-cyano-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,

4-[3-cyano-5-(4-methylthiophenyl)-1H-pyrazol-1-yl]benzenesulfonamide,

4-[5-(5-chloro-4-methoxyphenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide,

4-[5-(5-bromo-4-methoxyphenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide,

4-[3-cyano-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-[4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-[4-chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-bromo-5-(4-chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-(3,5-dichloro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-bromo-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-(3-chloro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-bromo-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-cyano-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-ethyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-methyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chlorophenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chlorophenyl)-4-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

4-[4-ethyl-5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-ethyl-5-(4-methoxy-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-ethyl-5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-ethyl-5-(3-fluoro-4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-fluorophenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-methyl-5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-fluoro-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-bromo-5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-(3,5-dichloro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-bromo-3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-(chloro-3-cyano-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-(4-chlorophenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-bromo-3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide,

4-[4-bromo-3-cyano-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide,
ethyl [1-(4-aminosulfonylphenyl)-4-bromo-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carboxylate,
methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-phenyl-1H-pyrazol-3-yl]carboxylate,
methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carboxylate,
ethyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carboxylate,
methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylate,
methyl [1-(4-aminosulfonylphenyl)-4-bromo-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylate,
methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(3-chloro-4-methoxyphenyl)-1H-pyrazol-3-yl]carboxylate,
methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(3,5-dichloro-4-methoxyphenyl)-1H-pyrazol-3-yl]carboxylate,
methyl [1-(4-aminosulfonylphenyl)-5-(3-bromo-4-methoxyphenyl)-4-chloro-1H-pyrazol-3-yl]carboxylate,
4-[4-chloro-3-isopropyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-3-methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-3-hydroxymethyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide,
4-[4-chloro-5-(chlorophenyl)-3-hydroxymethyl-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamid ,
4-[5-(4-fluoroph nyl)-3-(trifluoromethyl)-1H-pyrazol-

1-yl]benzenesulfonamide,
4-[5-(4-cyanophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-fluoro-2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-ethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3,5-dimethylphenyl-4-methoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamid ,
4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-

1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chloro-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-ethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2,4-dimethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methoxy-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-bromo-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-chloro-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3,4-dimethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-chloro-4-methoxy-5-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-ethyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-fluoro-2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methoxy-3-(3-propinyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3,5-dichloro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-chloro-4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benz nesulfonamide,

4-[5-(3-fluoro-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-methyl-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-chloro-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methyl-3-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-(N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-amino-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methylthiophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-phenyl-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-chloro-4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamid ,
4-[5-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)-

1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chloro-3-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3,4-dimethoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3,5-dichloro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3,5-difluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-bromo-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methylsulfonylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chlorophenyl)-3-(chloro-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-fluorophenyl)-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3,5-dichloro-4-methoxyphenyl)-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3-chloro-4-methoxyphenyl)-3-(chloromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-chlorophenyl)-3-(cyanomethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[3-(chloro-difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide,
ethyl 3-[1-(4-aminosulfonylphenyl)-5-(phenyl)-1H-

pyrazol-3-yl]2-cyano-2-propenoate,
4-[5-(phenyl)-3-(fluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(5-bromo-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(5-chloro-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(1-cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(1,4-benzodioxan-6-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[3-(difluoromethyl)-5-(4-methylcyclohexyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2-benzofuranyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(1,3-benzodioxol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2-benzofuryl-1)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(5-bromo-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(5-chloro-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(5-indanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(5-methyl-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(2,3-dihydrobenzofuran-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(1-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(1,2,3,4-tetrahydronaphth-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzen sulfonamide,

4-[5-(2-benzothienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(3,4-dihydro-2H-1-benzothiopyran-7-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
4-[5-(4-methyl-1,3-benzodioxol-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, and
4-[5-(4-methyl-1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-(4-fluorophenyl)-5-[4-methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
5-[4-(methylsulfonyl)phenyl)-1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-(methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-(methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-(methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,

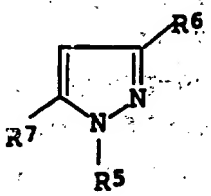
4-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,

1-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
1-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole,
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole,
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrazole,
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(methyl)-1H-pyrazole,
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(cyano)-1H-pyrazole,
1,4-bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,
5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl]-3-(difluoromethyl)-1H-pyrazole,
4-[4-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-5-yl)benzenesulfonamide,
4-[4-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-bromophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-iodophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-methylthiophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-methylsulfonylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

4-[4-(4-hydroxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-methoxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-nitrophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-aminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-N-methylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-N,N-dimethylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-trifluoromethylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-acetamidophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-[N-acetylamino]methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-fluorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-chlorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-bromophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-iodophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-methylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-methylthiophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-hydroxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-methoxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-nitrophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamid ,

4-[1-(4-aminophenyl)-4-ph nyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-N-methylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-N,N-dimethylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-trifluoromethylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1-(4-acetamidophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-fluorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-fluorophenyl)-1-phenyl-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-fluorophenyl)-1-phenyl-3-(methyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[4-(4-fluorophenyl)-1-phenyl-3-(cyano)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[1,4-bis(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide, and
4-[1,4-diphenyl-3-(difluorophenyl)-1H-pyrazol-5-yl]benzenesulfonamide.

Also preferable are the compounds as cycloxygenase inhibitors described in Japanese Patent Unexamined Publication (Kokai tokkyo koho) No. 246997/1993 (EP-0554829) or salts thereof. Those compounds described in said Kokai tokkyo koho are exemplified by the formula (IV) below.



(IV)

In th above formula (IV), R^5 is aryl which is substituted with substituent(s) select d from the group

consisting of C_{1-6} alkylthio, cyclo C_{1-6} alkyl, hydroxy, hydroxy C_{1-6} alkyl, cyano, C_{1-6} alkylenedioxy, acyl, acyloxy, aryloxy and C_{1-6} alkoxy optionally substituted with acyl or C_{1-6} alkoxy;

R^6 is halogen, halo C_{1-6} alkyl, cyano or acyl, and

R^7 is aryl substituted with nitro, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl or C_{1-6} alkylsulfonyl; provided that when R^7 is aryl substituted with nitro, hydroxy or lower alkoxy, then R^5 is aryl substituted with C_{1-6} alkylthio, C_{1-6} alkylsulfinyl or C_{1-6} alkylsulfonyl.

In the above formula (IV), R^5 is phenyl which is substituted with substituent(s) selected from the group consisting of hydroxy, hydroxy C_{1-6} alkyl, cyano, C_{1-6} alkylenedioxy, acyl, acyloxy, aryloxy and C_{1-6} alkoxy optionally substituted with acyl or C_{1-6} alkoxy, and preferably phenyl substituted with cyano, C_{1-6} alkanoyl or C_{1-6} alkoxy, and more preferably phenyl substituted with cyano or methoxy.

In the above formula (IV), R^7 is phenyl substituted with C_{1-6} alkylthio, C_{1-6} alkylsulfinyl or C_{1-6} alkylsulfonyl, preferably phenyl substituted with methylthio, methylsulfinyl or methylsulfonyl.

In the above formula (IV), R^6 is halogen or halo C_{1-6} alkyl, preferably bromine, difluoromethyl or trifluoromethyl.

Preferable examples of compounds represented by the formula (IV) is 3-(difluoromethyl)-1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole, or 3-(difluoromethyl)-1-(4-methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole.

Central analgesics generically refer to narcotic or non-narcotic analgesics; preferable examples include the following compounds and salts thereof.

Morphine, codeine, ethylmorphine, oxycodeine, dihydrocodeine, pethidine, fentanyl and pentazocine.

Steroids refer to all corticosteroids possessing anti-inflammatory activity; preferable examples include th following compounds and salts thereof.

Betamethasone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone and paramethasone.

Anti-inflammatory enzyme agents generically refer to proteins possessing acute inflammation-suppressing activity and/or analgesic activity; preferable examples include the following.

Bromelins, lysozyme, promelase, pronase, serrapeptase, streptokinase, chymotrypsin and amylase.

These anti-inflammatory analgesics may be in the form of pharmaceutically acceptable salts, as with compound (I).

The pharmaceutical composition of the present invention, comprising a combination of a quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic, can be administered orally or non-orally in the form of granules, powders, tablets, capsules, syrups, suppositories, injectable preparations, emulsions, elixirs, suspensions, solutions etc., as prepared separately or simultaneously by mixing with physiologically acceptable carriers, excipients, binders, diluents etc. When active ingredients are separately prepared, the resulting separate preparations can be administered in the form of a mixture with diluents etc. prepared freshly at the time of use; however, separate preparations may be administered to the same subject separately, simultaneously or at intervals.

The pharmaceutical composition of the present invention can be prepared as various dosage forms in accordance with ordinary methods. In the present specification, the term "non-oral" encompasses subcutaneous inj ction, intrav nous injection, intramuscular injection, intraperitoneal inj ction and drip infusion. Preparations for injection, e.g., aqueous or oily suspensions for

aseptic injection, can be prepared by methods known to those skilled in the art, using an appropriate dispersing agent or a wetting agent and a suspending agent. The preparation for aseptic injection may be a solution or suspension permitting aseptic injection in a diluent or solution that is non-toxic and administrable non-orally, such as an aqueous solution. Useful vehicles or solvents include water, Ringer's solution and isotonic saline. Aseptic nonvolatile oils can also be used as solvents or suspending media.

To this end, any nonvolatile oils or fatty acids can be used, including natural, synthetic or semi-synthetic fatty oils and fatty acids, and natural, synthetic or semi-synthetic mono-, di- or tri-glycerides.

Suppositories for rectal administration can be produced by mixing the drug and an appropriate non-irritative excipient that is solid at normal temperature but liquid at gut temperature and melts to release the drug in the rectum, such as cocoa butter or polyethylene glycol.

Solid dosage forms for oral administration include powders, granules, tablets, pills and capsules, as mentioned above. In such dosage forms, the active ingredient compound can be mixed with at least 1 additive selected from the group consisting of sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starches, agar, alginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatins, collagens, casein, albumin, and synthetic or semi-synthesis polymers and glycerides. As usual, these dosage forms can contain additional additives, including inert diluents, lubricants such as magnesium stearate, preservatives such as parabens and sorbic acid, antioxidants such as ascorbic acid, α-tocopherol and cysteine, disintegrating agents, binders, thickening agents, buffers, sweetening agents, flavoring agents and perfumes. Tablets and pills can also be produced with enteric coating. Liquid preparations for

oral administration include pharmaceutically acceptable emulsions, syrups, elixirs, suspensions and solutions, and may contain inert diluents in common use in the relevant art, such as water.

Although a daily dose of each pharmaceutical agent can be chosen appropriately, according to patient age, body weight, symptoms, administration time, dosage form, administration method, combination of each pharmaceutical agent etc., it can be chosen over the range of 5-1000 mg preferably 10-200 mg, per adult person, the likely clinical dose range for oral administration, and over the range of 0.1-100 mg, preferably 1-100 mg per adult person for non-oral adminstration in the case of quinoline or quinazoline compound for prophylaxis or therapy of arthritis; and can be increased or decreased as appropriate on the basis of the likely clinical dose range for oral administration in the case of rapidly acting anti-inflammatory analgesics such as ① cyclooxygenase inhibitors, ② central analgesics, ③ steroids, and ④ anti-inflammatory enzyme agents. In the case of oral or non-oral administration, the dose can be chosen as appropriate according to the situation on the basis of the likely clinical dose range when individual drugs are used singly.

① In the case of cyclooxygenase inhibitors, the dose for oral administration can be chosen over the range of 1-5000 mg, preferably 25-4500 mg per adult person, for example, 1000-4500 mg for aspirin, 50-150 mg for indomethachin, 25-75 mg for diclofenac, 60-180 mg for loxoprofen, and the dose for non-oral administration can be chosen over the range of 0.2-200 mg, preferably 1-100 mg per adult person.

② In the case of central analgesics, the dose for oral administration can be chosen over the range of 1-1000 mg, preferably 5-300 mg per adult person, for example, 10-60 mg for morphine, and the dose for non-oral administration can

be chosen over the range of 0.1-300 mg, preferably 0.5-100 mg per adult person for example, 5-60 mg, for morphine.

③ In the case of steroids, the dose for oral administration can be chosen over the range of 0.1-400 mg, preferably 0.5-100 mg per adult person, for example, 5-100 mg, for prednisolone, and 0.5-10 mg for dexamethasone, and the dose for non-oral administration can be chosen over the range of 0.1-100 mg, preferably 0.5-25 mg per adult person for example, 5-25 mg for prednisolone, 0.5-2.5 mg for dexamethasone.

④ In the case of anti-inflammatory enzyme agents, the dose for oral administration can be chosen over the range of 5-40 mg, per adult person.

Appropriate administration frequency is 1 to 3 times daily. A pharmaceutical composition of the present invention comprising a combination of the agents mentioned above has low toxity.

Example 1

Action on rat adjuvant arthritis

Male Lewis rats (7 weeks of age), 6 per group, were sensitized by intradermally injecting 0.05 ml of Freund's complete adjuvant (0.5% liquid paraffin suspension of dead tubercle bacillus cells) to the right hind leg paw. Five to 6 times weekly from just before sensitization (0 day) to 30 days, the ethyl ester of 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylic acid (Compound A) (3.13 mg/kg) and indomethacin (0.25 mg/kg), in suspension in 0.5% methyl cellulose, singly or concomitantly, were orally administered. Just before sensitization (0 day) and at 14 and 28 days, the left hind leg paw volume was measured to obtain the paw swelling suppression rate, in comparison with non-sensitized rats. Body weight was measured just before administration; the body weight increase rate (%) was obtain d in comparison with non-sensitized rats.

The results are shown in mean ± standard error for each group (N = 6) and compared by Student's t-test at a significance level of < 5%.

As shown in Table 1, concomitant administration of Compound A and indomethacin showed more potent action in terms of edema suppression and body weight increase, in comparison with either drug administered alone.

Particularly, with respect to the action in terms of edema suppression, which is a direct index of an anti-inflammatory action, the result of concomitant administration of compound A and indomethacin at 28 days showed a remarkable effect beyond the sum effect of both agents.

Table 1

Manner of Administration		Swelling Suppression Rate (%)		Body Weight Increase Rate (%)[1)]	
		14 Days	28 Days	14 Days	30 Days
Compound A	3.13	42	43	14*	24*
Indomethacin	0.25	38*	69*	11*	10
Concomitant use		64*Φ	95*Φα	15*	31*Φ

1)

$$\frac{\text{(Agent-administered rats)} - \text{(Sensitized control rats)}}{\text{(Normal control rats)} - \text{(Sensitized control rats)}} \times 100$$

*: $P < 0.05$ vs control group;
Φ: $P < 0.05$ vs indomethacin administration group
α: $P < 0.05$ vs compound A administration group

As seen in the table, concomitant use of Compound A and indomethacin showed greater swelling-suppressing action, in comparison with the single use of Compound A or indomethacin, resulting in markedly increased body weight. Especially, the effect of concomitant use of two compounds on the paw swelling at 28 days is additive or mor .

Industrial Applicability

The combined pharmaceutical provided by the present invention exhibits excellent rapidly acting and sustained anti-inflammatory analgesic action against arthritis, especially rheumatoid arthritis, with very low prevalence of side effects even in chronic administration, provided that drug combination, administration method, dose etc. are appropriately chosen according to symptoms.

CLAIMS

1. A pharmaceutical composition comprising a combination of a quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic agent.

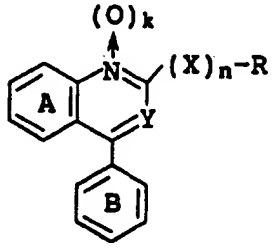
2. The pharmaceutical composition of claim 1, wherein said rapidly acting anti-inflammatory analgesic agent is a cyclooxygenase inhibitor.

3. The pharmaceutical composition of claim 1, wherein said rapidly acting anti-inflammatory analgesic agent is a central analgesic.

4. The pharmaceutical composition of claim 1, wherein said rapidly acting anti-inflammatory analgesic agent is a steroid.

5. The pharmaceutical composition of claim 1, wherein said rapidly acting anti-inflammatory analgesic agent is an anti-inflammatory enzyme agent.

6. The pharmaceutical composition of claim 1, wherein said quinoline or quinazoline compound for the prophylaxis or therapy of arthritis contains as an active ingredient a compound represented by the formula (I):



(I)

wherein Y represents a nitrogen atom or C-G (G represents a carboxyl group which may be esterified or amidated, an acyl, or a hydroxyalkyl group); R represents an optionally substituted hydrocarbon residue, or an optionally substituted heterocyclic group; X represents an oxygen atom or an optionally oxidized sulfur atom; n r presents 0 or 1;

k represents 0 or 1; G and R may bind together to form a ring; rings A and B may each have a substituent; or a pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition of claim 6, wherein n represents 0 and the optionally substituted hydrocarbon residue for R is a group represented by the formula: $-CH_2-X^1-Z^1$, wherein X^1 represents an oxygen atom, an optionally oxidized sulfur atom or $-(CH_2)_m-$ (m represents an integer from 0 to 5); Z^1 represents an optionally substituted hydrocarbon residue, an optionally substituted heterocyclic group or an optionally substituted amino group.

8. The pharmaceutical composition of claim 7, wherein X^1 is $-(CH_2)_m-$ (m is 0 or 1).

9. The pharmaceutical composition of claim 7, wherein the optionally substituted heterocyclic group for Z^1 is an aromatic 5-membered heterocyclic group containing 2 or 3 hetero atoms.

10. The pharmaceutical composition of claim 6, wherein Y is C-G.

11. The pharmaceutical composition of claim 10, wherein G is a C_{1-6} alkoxycarbonyl group.

12. The pharmaceutical composition of claim 10, wherein G is an ethoxycarbonyl group.

13. The pharmaceutical composition of claim 6, wherein ring A is substituted for by at least one alkoxy group.

14. The pharmaceutical composition of claim 6, wherein ring A is substituted for by two methoxy groups.

15. The pharmaceutical composition of claim 14, wherein ring A is substituted for by two methoxy groups respectively at the 6- and 7-positions of the quinoline ring or quinazoline ring.

16. The pharmaceutical composition of claim 6, wherein ring B is substituted for by at least one alkoxy group.

17. The pharmaceutical composition of claim 6, wherein ring B is substituted for by two identical or different alkoxy groups.

18. The pharmaceutical composition of claim 6, wherein k is 0.

19. The pharmaceutical composition of claim 6, wherein the compound represented by the formula (I) is

methyl 4-(3,4-dimethoxyphenyl)-2-ethyl-6,7-dimethoxyquinoline-3-carboxylate;

ethyl 6-chloro-2-methyl-4-(3,4-dimethoxyphenyl)quinoline-3-carboxylate;

6,7-dimethoxy-9-phenylfuro[3,4-b]quinoline-1(3H)-one;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline-3-carboxylate;

4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethylthiomethyl)-6,7-dimethoxyquinazoline;

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(4-methyl-1,2,4-triazol-3-yl)thiomethyl]quinazoline;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[2-(1-methylimidazol-2-yl)ethyl]quinoline-3-carboxylate;

methyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonylquinoline-2-acetate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-isopropoxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(4-hydroxy-3-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 7-hydroxy-6-methoxy-4-(3,4-dimethoxyphenyl)-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate 1-oxide; or

ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate.

20. A therapeutic agent for arthritis comprising a combination of a qunoline or quinazoline compound for the

prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic agent.

21. A method of treating an arthritis and/or an inflammation in mammals which comprises administering to the mammals a therapeutically effective amount of a quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic agent.

22. The method according to claim 21, wherein the quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and the rapidly acting anti-inflammatory analgesic agent are administered simultaneously.

23. The method according to claim 21, wherein the quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and the rapidly acting anti-inflammatory analgesic agent are administered sequentially.

24. Use of a combination of a quinoline or quinazoline compound for the prophylaxis or therapy of arthritis and a rapidly acting anti-inflammatory analgesic agent to manufacture a preparation for treating an arthritis and/or an infllamation in mammals.

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/JP 96/01102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/47 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP,A,0 339 485 (DU PONT) 2 November 1989 see claims 1,11; table 6 ---	1-5, 20-23 6-19,24
X Y	EP,A,0 468 789 (MERCK FROSST CANADA INC) 29 January 1992 see page 9, line 34 - page 11, line 48 ---	1-5, 20-23 6-19,24
X Y	EP,A,0 500 360 (MERCK FROSST CANADA INC) 26 August 1992 see page 8, line 11 - page 10, line 41; claim 6 ---	1-5, 20-23 6-19,24
Y,P	EP,A,0 686 630 (TAKEDA CHEMICAL INDUSTRIES LTD) 13 December 1995 cited in the application see the whole document --- -/--	6-19,24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 1996	22.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Foerster, W

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 96/01102

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 608 870 (TAKEDA CHEMICAL INDUSTRIES LTD) 3 August 1994 cited in the application see the whole document	6-19,24
Y	EP,A,0 567 107 (TAKEDA CHEMICAL INDUSTRIES LTD) 27 October 1993 cited in the application see the whole document	6-19,24

Form PCT/ISA/218 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern[illegible]al Application No
PCT/JP 96/01102

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0339485	02-11-89	US-A- 4966701	06-11-90
		AU-B- 628045	10-09-92
		AU-B- 3332189	02-11-89
		CA-A- 1333155	22-11-94
		DK-B- 170414	28-08-95
		JP-A- 1313428	18-12-89
		PT-B- 90363	31-08-94
		US-A- 5084462	28-01-92
EP-A-0468789	29-01-92	US-A- 5187180	16-02-93
		CA-A- 2047857	27-01-92
		JP-A- 6056831	01-03-94
EP-A-0500360	26-08-92	AU-B- 648385	21-04-94
		AU-B- 1111992	27-08-92
		CA-A- 2061675	22-08-92
		CN-A- 1065062	07-10-92
		JP-A- 5025135	02-02-93
		JP-B- 7088361	27-09-95
		US-A- 5212180	18-05-93
EP-A-0686630	13-12-95	CA-A- 2151088	08-12-95
		JP-A- 8053419	27-02-96
EP-A-0608870	03-08-94	AU-B- 5474294	04-08-94
		CA-A- 2114300	29-07-94
		CN-A- 1105363	19-07-95
		FI-A- 940414	29-07-94
		HU-A- 70194	28-09-95
		JP-A- 7118266	09-05-95
		NO-A- 940245	29-07-94
		NZ-A- 250761	28-03-95
		US-A- 5436247	25-07-95
EP-A-0567107	27-10-93	AU-B- 3699193	28-10-93
		CA-A- 2094774	25-10-93
		CN-A- 1079222	08-12-93
		HU-A- 64322	28-12-93
		JP-A- 6306052	01-11-94
		NZ-A- 247477	26-07-95